(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 February 2002 (28.02.2002)

PCT

(10) International Publication Number
WO 02/15892 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/EP01/09586

(22) International Filing Date: 20 August 2001 (20.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/643,642 22 August 2000 (22.08.2000) US

(71) Applicant *(for all designated States except AT, US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant *(for AT only)*: **NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H.** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ALLISON, Malcolm** [GB/CH]; Grenzacherstrasse 108, CH-058 Basel (CH). **GATLIN, Marjorie, Regan** [US/US]; 913 Lovering Avenue, Wilmington, DE 19806 (US).

(74) Agent: **BECKER, Konrad**; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/15892 A2

(54) Title: COMBINATIONS

(57) Abstract: The present invention relates to a combination, especially a pharmaceutical composition, comprising (a) an insulin secretion enhancer or a pharmaceutically acceptable salt thereof and (b) at least one of the active ingredients selected from the group consisting of (i) HMG-Co-A reductase inhibitors or a pharmaceutically acceptable salt thereof; and (ii) ACE inhibitors or a pharmaceutically acceptable salt thereof; and, in case of a pharmaceutical composition, a pharmaceutically acceptable carrier.

Combinations

The present invention relates to a combination, especially a pharmaceutical composition, comprising

(a) an insulin secretion enhancer or a pharmaceutically acceptable salt thereof and

(b) at least one of the active ingredients selected from the group consisting of

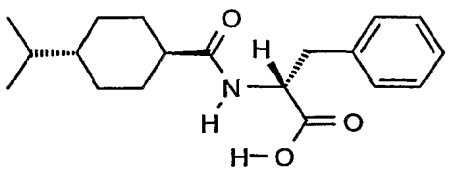
(i) HMG-Co-A reductase inhibitors or a pharmaceutically acceptable salt thereof; and

(ii) ACE inhibitors or a pharmaceutically acceptable salt thereof; and,

in case of a pharmaceutical composition, a pharmaceutically acceptable carrier.

Insulin secretion enhancers are active ingredients that have the property to promote the secretion of insulin from pancreatic β-cells. Examples of insulin secretion enhancers are sulfonylureas (SU), especially those which promote the secretion of insulin from pancreatic β-cells by transmitting signals of insulin secretion via SU receptors in the cell membrane, including (but are not limited to) tolbutamide; chlorpropamide; tolazamide; acetohexamide; 4-chloro-N-[(1-pyrolidinylamino)carbonyl]-benzensulfonamide (glycopyramide); glibenclamide (glyburide); gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; and tolylcyclamide, or a pharmaceutically acceptable salt thereof.

Insulin secretion enhancers furthermore include short-acting insulin secretion enhancers, such as the new phenylalanine derivative nateglinide [N-(trans-4-isopropylcyclohexyl-carbonyl)-D-phenylalanine] (cf. EP 196222 and EP 526171) of the formula



(I);

repaglinide [(S)-2-ethoxy-4-{2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl}benzoic acid – cf. EP 589874] ; calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinlycarbonyl)-propionate dihydrate (mitiglinide – cf. EP 507534); furthermore

representatives of the new generation of SUs such as glimepiride (cf. EP 31058); and in free or pharmaceutically acceptable salt form.

Insulin secretion enhancers likewise include the long-acting insulin secretion enhancer DPP-IV inhibitors, GLP1 and GLP1 agonists.

DPP-IV is responsible for inactivating GLP-1. More particularly, DPP-IV generates a GLP-1 receptor antagonist and thereby shortens the physiological response to GLP-1. GLP-1 is a major stimulator of pancreatic insulin secretion and has direct beneficial effects on glucose disposal.

The DPP-IV inhibitor can be peptidic or, preferably, non-peptidic. DPP-IV inhibitors are in each case generically and specifically disclosed e.g. in WO 98/19998, DE 196 16 486 A1, WO 00/34241 and WO 95/15309, in each case in particular in the compound claims and the final products of the working examples, the subject-matter of the final products, the pharmaceutical preparations and the claims are hereby incorporated into the present application by reference to these publications. Preferred are those compounds that are specifically disclosed in Example 3 of WO 98/19998 and Example 1 of WO 00/34241, respectively.

GLP-1 is a insulinotropic proteine which was described, e.g., by W.E. Schmidt et al. in Diabetologia 28, 1985, 704-707 and in US 5,705,483.

The term "GLP-1 agonists" used herein means variants and analogs of GLP-1(7-36)NH_2 which are disclosed in particular in US 5,120,712, US 5,118666, US 5,512,549, WO 91/11457 and by C. Orskov et al in J. Biol. Chem. 264 (1989) 12826. The term "GLP-1 agonists" comprises especially compounds like GLP-1(7-37), in which compound the carboxy-terminal amide functionality of Arg^{36} is displaced with Gly at the 37^{th} position of the GLP-1(7-36)NH_2 molecule and variants and analogs thereof including GLN^9-GLP-1(7-37), D-GLN^9-GLP-1(7-37), acetyl LYS^9-GLP-1(7-37), LYS^{18}-GLP-1(7-37) and, in particular, GLP-1(7-37)OH, VAL^8-GLP-1(7-37), GLY^8-GLP-1(7-37), THR^8-GLP-1(7-37), MET^8-GLP-1(7-37) and 4-imidazopropionyl-GLP-1. Special preference is also given to the GLP agonist analog exendin-4, described by Greig et al in Diabetologia 1999, 42, 45-50.

A preferred insulin secretion enhancer is repaglinide, most preferred is nateglinide.

The term nateglinide likewise comprises crystal modifications such as disclosed in EP 0526171 B1 or US 5,488,510, respectively, the subject matter of which, especially with respect to the identification, manufacture and characterization of crystal modifications, is herewith incorporated by reference to this application, especially the subject matter of claims 8 to 10 (H-form crystal modification) as well as the corresponding references to the B-form crystal modification.

The term "short-acting insulin secretion enhancer" comprises corresponding agents with a maximum secretion of insulin that is attained within one hour, preferably within 30 minutes, after the administration of the agent, most preferably within 20 minutes having a biological half-life, T ½, of less than two hours, preferably, 1.5 hours. The term long-acting insulin secretion enhancer" comprises corresponding agents with a maximum secretion of insulin that is attained more than one hour after administration of the agent.

HMG-Co-A reductase inhibitors (also called β-hydroxy-β-methylglutaryl-co-enzyme-A reductase inhibitors) are understood to be those active agents that may be used to lower the lipid levels including cholesterol, especially LDL-cholesterol, in blood.

The class of HMG-Co-A reductase inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds that are selected from the group consisting of atorvastatin (cf. EP 680320), cerivastatin (cf. EP 491226), fluvastatin (cf. US 5354772), pitavastatin (cf. EP 304063), lovastatin (cf. EP 22478), pravastatin (cf. UK 2077264), rosuvastatin (ZD 4522or S 4522) and simvastatin (cf. EP 33538), or, in each case, a pharmaceutically acceptable salt thereof.

Preferred HMG-Co-A reductase inhibitors are those agents that have been marketed, most preferred is fluvastatin, atorvastatin, pitavastatin or simvastatin or, in each case, a pharmaceutically acceptable salt thereof.

The interruption of the enzymatic degradation of angiotensin I to angiotensin II with so-called ACE-inhibitors (also called angiotensin converting enzyme inhibitors) is a successful

variant for the regulation of blood pressure and thus also makes available a therapeutic method for the treatment of congestive heart failure.

The class of ACE inhibitors comprises compounds having differing structural features. For example, mention may be made of the compounds which are selected from the group consisting alacepril (cf. EP 7477), benazepril (cf. EP 72352), benazeprilat (cf. EP 72352), captopril (cf. US 4105776), ceronapril (cf. EP 229520), cilazapril (cf. EP 94095), delapril (cf. EP 51391), enalapril (cf. EP 12401), enaprilat (cf. EP 12401), fosinopril (cf. EP 53902), imidapril (cf. EP 95163), lisinopril (cf. EP 12401), moveltipril (cf. ZA 82/3779), perindopril (cf. EP 49658), quinapril (cf. EP 49605), ramipril (cf. EP 79022), spirapril (cf. EP 50800), temocapril (cf. EP 161801), and trandolapril (cf. EP 551927), or, in each case, a pharmaceutically acceptable salt thereof.

Preferred ACE inhibitors are those agents that have been marketed, most preferred are benazepril and enalapril.

Especially preferred is a combination nateglinide or a pharmaceutically acceptable salt thereof and fluvastation, pitavastatin and simvastatin or, in each case, a pharmaceutically acceptable salt thereof. Furthermore, a combination of nateglinide or a pharmaceutically acceptable salt thereof and benazepril, benzeprilat, enalapril or enalaprilat or, in each case a pharmaceutically acceptable salt thereof is preferred.

The corresponding active ingredients or pharmaceutically acceptable salts thereof may also be used in form of a solvate, such as a hydrate or including other solvents, used for crystallization.

The corresponding active ingredients or a pharmaceutically acceptable salts thereof may also be used in form of a solvate, such as a hydrate or including other solvents, used for crystallization.

The structure of the active agents identified by generic or tradenames may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify

the active agents and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both in vitro and in vivo.

The combination according to the present invention comprises
(1) both an insulin secretion enhancer or a pharmaceutically acceptable salt thereof and at least one HMG-Co-A reductase inhibitor; or
(2) both an insulin secretion enhancer or a pharmaceutically acceptable salt thereof and at least one ACE inhibitor or a pharmaceutically acceptable salt thereof; or
(3) an insulin secretion enhancer or a pharmaceutically acceptable salt thereof and at least one HMG-Co-A reductase inhibitor of a pharmaceutically acceptable salt thereof and at least one ACE inhibitor or a pharmaceutically acceptable salt thereof.

The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having an acid group (for example COOH) can also form salts with bases.

The pharmaceutical activities as effected by administration of representatives of the class of insulin secretion enhancers, HMG-Co-A reductase inhibitors or ACE inhibitors respectively, or of the combination of active agents used according to the present invention can be demonstrated e.g. by using corresponding pharmacological models known in the pertinent art. The person skilled in the pertinent art is fully enabled to select a relevant animal test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects.

To evaluate the antihypertensive activity of the combination according to the invention, for example, the methodology as described by Lovenberg W: Animal models for hypertension research. Prog. Clin. Biol. Res. 1987, 229, 225-240 may be applied. For the evaluation that the combination according to the present invention may be used for the treatment of congestive heart failure, for example, the methods as disclosed by Smith HJ, Nuttall A: Experimental models of heart failure. Cardiovasc Res 1985, 19, 181-186 may be applied. Molecular approaches such as transgenic methods are also described, for example by Luft

et al.: Hypertension-induced end-organ damage. A new transgemic approach for an old problem. Hypertension 1999, 33, 212-218.

The insulin secretion enhancing properties of the combination according to the present invention may be determined by following the methodology as disclosed, for example, in the publication of T.Ikenoue et al. Biol.Pharm.Bull. 29(4), 354-359 (1997).

The corresponding subject matter of these four references is herewith incorporated by reference in this specification.

To evaluate the HMG-Co-A reductase inhibitory activities of the combination according to the invention, for example, may be determined by following the methodology as disclosed, for example, in US 4,739,073 or US 5,354,772, respectively. The corresponding subject matter of these two references is herewith incorporated by reference in this specification.

Accordingly, the combination according to the present invention may be used, e.g., for the treatment of diseases and disorders associated with conversion of angiotensin I to angiotensin II and with hypoglycemia. Especially, the combination according to the present invention may be used e.g., for the prevention, delay of progression or treatment of diseases and disorders selected from the group consisting of hyperglycemia, hyperinsulinaemia, hyperlipidaemia, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, obesity, diabetic retinopathy, macular degeneration, cataracts, diabetic nephropathy, glomerulosclerosis, diabetic neuropathy, erectile dysfunction, premenstrual syndrome, coronary heart disease, hypertension, especially ISH, angina pectoris, myocardial infarction, stroke, vascular restenosis, endothelial dysfunction, impaired vascular compliance, skin and connective tissue disorders, foot ulcerations and ulcerative colitis. Preferably, said combination may be used for the treatment of hypertension, especially ISH, congestive heart failure, endothelial dysfunction, impaired vascular compliance, hyperlipidaemia, hyperglycemia, hyperinsulinaemia, and type II diabetes mellitus.

A "disease or condition which may be inhibited by the enhancement of insulin secretion" as defined in this application comprises, but is not limited to hyperglycemia, hyperinsulinaemia, hyperlipidaemia, insulin resistance, impaired glucose metabolism, conditions of impaired

glucose tolerance (IGT), conditions of impaired fasting plasma glucose, obesity, diabetic retinopathy, macular degeneration, cataracts, diabetic nephropathy, glomerulosclerosis, diabetic neuropathy, erectile dysfunction, premenstrual syndrome, coronary heart disease, hypertension, angina pectoris, myocardial infarction, stroke, vascular restenosis, skin and connective tissue disorders, foot ulcerations and ulcerative colitis.

A "disease or condition which may be inhibited by HMG-Co-A reductase" as defined in this application comprises, but is not limited to hyperlipidaemia.

A "disease or condition which may be inhibited by the inhibition of angiotensin converting enzyme" as defined in this application comprises, but is not limited to hypertension, congestive heart failure, diabetes, especially type 2 diabetes mellitus, diabetic retinopathy, macular degeneration, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, syndrome X, premenstrual syndrome, coronary heart disease, angina pectoris, myocardial infarction, stroke, vascular restenosis, and the like.

Hypertension, especially in connection with a "disease or condition which may be inhibited by the inhibition of angiotensin converting enzyme", a "disease or condition which may be inhibited by the enhancement of insulin secretion", a "disease or condition which may be inhibited by HMG-Co-A reductase" includes and is not limited to mild, moderate and severe hypertension as defined in Journal of Hypertension 1999, 17:151-183, especially on page 162. Especially preferred is "isolated systolic hypertension" (ISH).

Preferably, the jointly therapeutically effective amounts of the active agents according to the combination of the present invention can be administered simultaneously or sequentially in any order, e.g. separately or in a fixed combination.

Under certain circumstances, drugs with different mechanisms of action may be combined. However, just considering any combination of drugs having different modes of action but acting in the similar field does not necessarily lead to combinations with advantageous effects.

All the more surprising is the experimental finding that the combined administration of an insulin secretion enhancer with a HMG-Co A reductase inhibitor and/or an ACE inhbitor and

and or, in each case, a pharmaceutically acceptable form thereof, results not only in a beneficial, especially a potentiating or a synergistic, therapeutic effect. Independent thereof, additional benefits resulting from combined treatment can be achieved such as a surprising prolongation of efficacy, a broader variety of therapeutic treatment and surprising beneficial effects on diseases and conditions associated with diabetes, e.g. less gain of weight.

The term "potentiation" shall mean an increase of a corresponding pharmacological activity or therapeutical effect, respectively. Potentiation of one component of the combination according to the present invention by co-administration of an other component according to the present invention means that an effect is being achieved that is greater than that achieved with one component alone or that is greater than the sum of effects of each component.

The term "synergistic" shall mean that the drugs, when taken together, produce a total joint effect that is greater than the sum of the effects of each drug when taken alone.

ISH is the most common form of hypertension in people over 50 years. It is defined as elevated systolic blood pressure (above 140 mm Hg) in conjunction with normal diastolic blood pressure (below 90 mm Hg). Elevated systolic blood pressure is an independent risk factor for cardiovascular diseases and may lead e.g. to myocardial hypertrophy and heart failure. ISH is furthermore characterized by an increased pulse pressure, defined as the difference between systolic and diastolic blood pressures. Elevated pulse pressure is being recognized as the type of hypertension the least likely to be well controlled. A reduction of elevated systolic blood perssure and correspondingly of pulse pressure is associated with a significant risk reduction in cardiovascular death. It has surprisingly been found that the combination of an ACE inhibitor and an insulin secretion enhancer leads to a decrease of ISH and pulse rate, both in hypertensive patients having type 2 diabetes mellitus and in hypertensive patient that do not have type 2 diabetes mellitus.

Furthermore, it has been found that the chronic co-administration of either an insulin sensitizer or an insulin secretion enhancer imparts the beneficial effect on blood vessel morphology and function and results in a decrease of vascular stiffness and correspondingly in a maintenance and in an improvement of vascular compliance.

Accordingly, it has been found that the addition of an ACE inhibitor to that of an insulin secretion enhancer would potentiate the effect on systolic blood pressure and further improve vascular stiffness/compliance. Conversely, the proven antihypertensive effects of an ACE inhibitor on systolic and diastolic blood pressure may be potentiated by the addition of an insulin secretion enhancer. The benefit of these combinations may also extend to an additional or potentiated effect on endothelial function, and improve vascular function and structure in various organs/tissues including the kidney, heart, eye and brain. Through the reduction in glucose levels, an anti-thrombotic and anti-atherosclerotic effect cany also be demonstrated. Reduction of glucose would prevent or minimize the glycosylation of any structural or functional protein within the cardio-renal system. This effect may prove to be highly beneficial by evoking an additive or synergistic effect on vascular function/structure when administered with an ACE inhibitor which alone improves cardiovascular function and structure through a distinct mechanism.

Further benefits are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used in order to diminish the incidence of side effects. This is in accordance with the desires and requirements of the patients to be treated.

For example, it has turned out that the combination according to the present invention provides benefit especially in the treatment of modest hypertension that is beneficial to all diabetic patients regardless of their hypertensive status, e.g. reducing the risk of negative cardiovascular events by two different modes of action.

The ACE inhibitors have proven to be also useful in the treatment of type 2 diabetes mellitus beyond the reduction of blood pressure. At sub-therapeutic doses, with respect to the treatment of hypertension, the combination according to the invention may be merely used for the treatment of diabetes, especially type 2 diabetes mellitus. In view of the reduced dose of the ACE inhibitors, there is a considerable safety profile of the combination making it suitable for first line therapy.

The present invention relates to the use of a pharmaceutical composition of at least two therapeutic agents selected from the group consisting of the active ingredients

(a) an insulin secretion enhancer or a pharmaceutically acceptable salt thereof and

(b) at least one of the active ingredients selected from the group consisting of

(i) HMG-Co-A reductase inhibitor or a pharmaceutically acceptable salt thereof; and

(ii) ACE inhibitors or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for the prevention, delay of progression or treatment of a disease and disorder which may be inhibited by the enhancement of insulin secretion, by the inhibition of an ACE inhibitor and/or by the inhibition of HMG-CoA reductase, for example, for the prevention, delay of progression or treatment of hypertension, e.g. modest hypertension, especially ISH, endothelial dysfunction, impaired vascular compliance, hyperglycemia, hyperinsulinaemia, congestive heart failure, hyperlipidaemia and type II diabetes mellitus.

The present invention also relates to a method for the prevention, delay of progression or treatment of a disease and disorder which may be inhibited by the enhancement of insulin secretion, the inhibition of an ACE inhibitor and/or by the inhibition of HMG-CoA reductase comprising administering to a warm-blooded animal, including man, in need thereof jointly therapeutically effective amounts of at least two therapeutic agents selected from the group consisting of the active ingredients

(a) an insulin secretion enhancer or a pharmaceutically acceptable salt thereof and

(b) at least one of the active ingredients selected from the group consisting of

(i) HMG-Co-A reductase inhibitors or a pharmaceutically acceptable salt thereof; and

(ii) ACE inhibitors or a pharmaceutically acceptable salt thereof.

The pharmaceutical composition according to the present invention as described hereinbefore and hereinafter may be used for simultaneous use or sequential use in any order, e.g. for separate use or as a fixed combination.

The pharmaceutical composition according to the present invention comprises a "kit of parts" in the sense that the components can be dosed independently or by use of different fixed combinations with distinguished amounts of the components at different time points.

The parts of the "kit of parts" can then e.g. be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the "kit of parts". Preferably, the time intervals are chosen such that the effect on the treated disease or condition in the combined use of the parts is larger than the effect that would be obtained by use of only any one of the components. Preferably, there is at least one beneficial effect, e.g. a mutual enhancing of the effect of
at least two therapeutic agents selected from the group consisting of the active ingredients

(a) an insulin secretion enhancer or a pharmaceutically acceptable salt thereof and

(b) at least one of the active ingredients selected from the group consisting of

(i) HMG-Co-A reductase inhibitors or a pharmaceutically acceptable salt thereof; and

(ii) ACE inhibitors or a pharmaceutically acceptable salt thereof;

in particular a potentiation or a synergism, e.g. a more than additive effect, additional advantageous effects, less side effects, a combined therapeutical effect in a non-effective dosage of one or each of the components, especially a potentiation or a strong synergism.

The invention furthermore relates to a commercial package comprising the combination according to the present invention together with instructions for simultaneous, separate or sequential use.

These pharmaceutical preparations are for enteral, such as oral, and also rectal or parenteral, administration to homeotherms, with the preparations comprising the pharmacological active compound either alone or together with customary pharmaceutical auxiliary substances. For example, the pharmaceutical preparations consist of from about 0.1 % to 90 %, preferably of from about 1 % to about 80 %, of the active compound. Pharmaceutical preparations for enteral or parenteral, and also for ocular, administration are, for example, in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner that is known per se, for example using conventional mixing, granulation, coating, solubulizing or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compound with solid excipients, if desired granulating a mixture which has been obtained, and, if required or necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

Preferred dosages for the active ingredients of the pharmaceutical combination according to the present invention are therapeutically effective dosages, especially those that are commerically available.

Normally, in the case of oral administration, an approximate daily dose of from about 1 mg to about 360 mg is to be estimated e.g. for a patient of approximately 75 kg in weight.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

The insulin secretion enhancer nateglinide (I) is preferably administered to the warm-blooded animal in a dosage in the range of about 5 to 1200, more preferably 25 to 800, mg/day, when the warm-blooded animal is a human of about 70 kg body weight. Preferred dosages contain 30mg, 60mg or 120mg of nateglinde to be administered preferably before the main meals. Depending on the number of main meals the dose regimen are two times a day (BID) or three times a day (TID) or four times a day (QID).

The insulin secretion enhancer repaglinde is preferably administered in a dosage range of about 0.01 mg to about 8 mg, more preferred from about 0.5 to about 6 mg.

In case of HMG-Co-A reductase inhibitors , preferred dosage unit forms of HMG-Co-A reductase inhibitors are, for example, tablets or capsules comprising e.g. from about 5 mg to about 120 mg, preferably, when using fluvastatin, for example, 20 mg, 40 mg or 80 mg (equivalent to the free acid) of fluvastatin, for example, administered once a day.

In case of ACE inhibitors, preferred dosage unit forms of ACE inhibitors are, for example, tablets or capsules comprising e.g. from about 5 mg to about 20 mg, preferably 5 mg, 10 mg, 20 mg or 40 mg, of benazepril; from about 6.5 mg to 100 mg, preferably 6.25 mg, 12.5 mg, 25 mg, 50 mg, 75 mg or 100 mg, of captopril; from about 2.5 mg to about 20 mg, preferably 2.5 mg, 5 mg, 10 mg or 20 mg, of enalapril; from about 10 mg to about 20 mg, preferably 10 mg or 20 mg, of fosinopril; from about 2.5 mg to about 4 mg, preferably 2 mg

or 4 mg, of perindopril; from about 5 mg to about 20 mg, preferably 5 mg, 10 mg or 20 mg, of quinapril; or from about 1.25 mg to about 5 mg, preferably 1.25 mg, 2.5 mg, or 5 mg, of ramipril. Preferred is t.i.d. administration.

Especially preferred are low dose combinations.

The following examples illustrate the above-described invention; however, it is not intended to restrict the scope of this invention in any manner.

Example 1:

108,000 tablets, each which contain 120 mg of nateglinide are prepared as follows:

Composition:	nateglinide	12.960 kg
	lactose, NF	30.564 kg
	microcrystalline cellulose, NF	15.336 kg
	povidone, USP	2.592 kg
	croscarmellose sodium, NF	3.974 kg
	colloidal silicon dioxide, NF	1.382 kg
	magnesium stearate, NF	1.231 kg
	coating: opadry yellow	1.944 kg
	purified water, USP*	Q.S.

*: *removed during process*

Preparation process: The microcrystalline cellulose, povidone, part of the croscarmellose sodium, nateglinide and lactose are mixed in a high shear mixer and afterwards granulated using purified water. Alternatively, the microcrystalline cellulose, povidone, a portion of the croscarmellose sodium, nateglinide and lactose are granulated in a collette gral granulator with the addition of purified water. The wet granules are dried in a fluid bed dryer and passed through a screen. The colloidal silicon dioxide and the rest of the croscarmellose sodium are mixed, passed through a screen and blended with the dried granules in a V-blender. The magnesium stearate is passed through a screen, blended with the blend from the V-blender and afterwards the total mixture is compressed to tablets. The opadry yellow is suspended in purified water and the tablets are coated with the coating suspension.

Examples 2-4:

Component	**60mg**	**120mg**	**180mg**
Starlix (H-form crystal modification) Drug Substance (DS)	60	120	180
Lactose Monohydrate	141.5	283	214
MicrocrystallineCellulose	71	142	107
Povidone K30	12	24	23
Croscarmellose Sodium	12	24	34
Sub-Total (Granulation)	**296.5**	**593**	**558**
Croscarmellose Sodium	6.4	12.8	24.5
Colloidal Silicone Dioxide	6.4	12.8	12.3
Magnesium Stearate	5.7	11.4	15.2
Sub-Total (Core)	**(315)**	**(630)**	**(610)**
Opadry	9	18	18
Total	**324**	**648**	**628**

Example 5:

Hard gelatin capsule:

Component	Amount per unit [mg]
Capsule	
Fluvastatin Sodium [1)]	21.481 [2)]
Calcium Carbonate	62.840
Sodium Bicarbonate	2.000
Microcrystalline Cellulose	57.220
Pregelatinized Starch	41.900
Purified Water [3)]	Q.S.
Magnesium Stearate	1.050
Talc	9.430

Target Capsule Fill Weight	195.92
Capsule Shell	
Hard gelatin Capsule Shell	48.500
Branding Ink (pre-printed)	
White Ink	Trace
Red Ink	Trace
Target Capsule Weight	244.42

[1] includes a 2% overage for moisture

[2] 20 mg of free acid is equivalent to 21.06 mg Na salt

[3] partially removed during processing

Example 6:

Hard gelatin capsule

Component	Amount per unit [mg]
Fluvastatin Sodium	42.962 [1) 2)]
Calcium Carbonate	125.680
Sodium Bicarbonate	4.000
Microcrystalline Cellulose	114.440
Pregelatinized Starch	83.800
Purified Water [3)]	Q.S.
Magnesium Stearate	2.100
Talc	18.860
Target Capsule Fill Weight	391.840
Capsule Shell	
Hard gelatin Capsule Shell	76.500
Branding Ink (pre-printed)	
White Ink	Trace
Red Ink	Trace
Target Capsule Weight	468.34

[1] includes a 2% overage for moisture

[2] 20 mg of free acid equivalent to 21.06 mg Na salt

[3] partially removed during processing

Example 7:

Round, slightly bi-convex, film-coated tablets with beleved edges:

Component	Amount per unit [mg]
Table Core	
Fluvastatin Sodium [1)]	84.24 [2)]
Cellulose Microcrystalline / Micro-crystalline cellulose fine powder	111.27
Hypromellose / Hydroxypropyl methyl cellulose (Methocel K100LVP CR; HPMC100 cps)	97.50
Hydroxypropyl cellulose (Klucel HXF)	16.25
Potassium hydrogen carbonate / Potassium bicarbonate	8.42
Povidone	4.88
Magnesium stearate	2.44
Core Tablet Weight	325.00
Coating	
Coating premix - Opadry Yellow (00F22737)	9.75
Total Weight	334.75
Water, purified [3)]	Q.S.

[1)] 84.24 mg of the sodium salt of fluvastatin is equivalent to 80 mg of fluvastatin free acid

[2)] to be adjusted for moisture (LOD)

[3)] removed during processing

Example 8:

Round, biconvex, beveled-edged, film-coated tablets

Component	Unit wt./Vol. [mg]	Unit wt./Vol. [mg]	Unit wt./Vol. [mg]	Unit wt./Vol. [mg]
Benazepril Hydrochloride	5.00	10.00	20.00	40.00
Lactose Monohydrate, NF	142.00	132.00	117.00	97.00
Pregelatinized Starch, NF	8.00	8.00	8.00	8.00
Colloidial Silicon Dioxide, NF (Cab-O-Sil, M-5)	1.00	1.00	1.00	1.00
Crospovidone, NF	3.00	3.00	3.00	3.00
Microcrystalline Cellulose, NF	18.00	18.00	18.00	24.25
Hydrogenated Castor Oil, NF	8.00	8.00		
Magnesium Stearate, NF			8.00	1.75
Color:	-			0.50
Yellow-Brown (suspension)		2.00		
Red-Brown (suspension)			0.50	
Purified Water, USP	trace	trace	trace	trace
Opadry Color:				
Yellow	8.38	8.38		
Pink			8.38	8.38
Total	193.38	190.38	183.88	183.88

What is claimed is

1. A pharmaceutical composition, comprising
(a) an insulin secretion enhancer or a pharmaceutically acceptable salt thereof and
(b) at least one of the active ingredients selected from the group consisting of
(i) HMG-Co-A reductase inhibitors or a pharmaceutically acceptable salt thereof; and
(ii) ACE inhibitors or a pharmaceutically acceptable salt thereof; and
a pharmaceutically acceptable carrier.

2. A composition according to claim 1 wherein the insulin secretion enhancer is selected from tolbutamide; chlorpropamide; tolazamide; acetohexamide; glycopyramide; glibenclamide; gliclazide; 1-butyl-3-metanilylurea; carbutamide; glibonuride; glipizide; gliquidone; glisoxepid; glybuthiazole; glibuzole; glyhexamide; glymidine; glypinamide; phenbutamide; tolylcyclamide, nateglinide repaglinide; mitiglinide; and glimepiride; or, in each case, a pharmaceutically acceptable salt thereof.

3. A composition according to claim 1 wherein the insulin secretion enhancer is nateglinide or a pharmaceutically acceptable salt thereof.

4. A composition according to claim 1 wherein the HMG-Co-A reductase inhibitor is selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, pitavastatin, lovastatin, pravastatin, rosuvastatin and simvastatin, or, in each case, a pharmaceutically acceptable salt thereof.

5. A composition according to claim 4 wherein the HMG-Co-A reductase inhibitor is atorvastatin, pitavastatin or fluvastatin, or, in each case, a pharmaceutically acceptable salt thereof.

6. A composition according to claim 1 wherein the ACE inhibitor is selected from the group consisting of alacepril, benazepril, benazeprilat, captopril, ceronapril, cilazapril, delapril, enalapril, enaprilat, fosinopril, imidapril, lisinopril, moveltipril, perindopril), quinapril,

ramipril, spirapril, temocapril, and trandolapril, or, in each case, a pharmaceutically acceptable salt thereof.

7. A composition according to claim 6 wherein the ACE inhibitor is benazepril or enalapril, or, in each case, a pharmaceutically acceptable salt thereof.

8. A composition according to any one of claims 1 to 7 for the prevention, delay of progression or treatment of a of disease and disorder selected from the group consisting of hyperglycemia, hyperinsulinaemia, hyperlipidaemia, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, obesity, diabetic retinopathy, macular degeneration, cataracts, diabetic nephropathy, glomerulosclerosis, diabetic neuropathy, erectile dysfunction, premenstrual syndrome, coronary heart disease, hypertension, especially ISH, angina pectoris, myocardial infarction, stroke, vascular restenosis, endothelial dysfunction, impaired vascular compliance, skin and connective tissue disorders, foot ulcerations and ulcerative colitis.

9. A composition according to claim 8 for the prevention, delay of progression or treatment of a of disease and disorder selected from the group consisting of hypertension, especially ISH, congestive heart failure, endothelial dysfunction, impaired vascular compliance, hyperlipidaemia, hyperglycemia, hyperinsulinaemia, and type II diabetes mellitus.

10. A method for the prevention, delay of progression or treatment of a disease and disorder which may be inhibited by the enhancement of insulin secretion, the inhibition of an ACE inhibitor and/or by the inhibition of HMG-CoA reductase comprising administering to a warm-blooded animal, including man, in need thereof jointly therapeutically effective amounts of at least two therapeutic agents selected from the group consisting of the active ingredients

(a) an insulin secretion enhancer or a pharmaceutically acceptable salt thereof and

(b) at least one of the active ingredients selected from the group consisting of

(i) HMG-Co-A reductase inhibitors or a pharmaceutically acceptable salt thereof; and

(ii) ACE inhibitors or a pharmaceutically acceptable salt thereof.

11. Use of a combination comprising

(a) an insulin secretion enhancer or a pharmaceutically acceptable salt thereof and

(b) at least one of the active ingredients selected from the group consisting of

(i) HMG-Co-A reductase inhibitors or a pharmaceutically acceptable salt thereof; and

(ii) ACE inhibitors or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for the prevention, delay of progression or treatment of a disease and disorder which may be inhibited by the enhancement of insulin secretion, the inhibition of an ACE inhibitor and/or by the inhibition of HMG-CoA reductase.